1. Cigarettes Are Combination Products

By weight, the drug nicotine is only a small part of a cigarette.[1144] First, the cigarette also has components that together constitute an "instrument, implement, . . . contrivance or similar or related article" under the Act. As a cigarette manufacturer has acknowledged, cigarettes are "a highly engineered product."[1145] They have components that have been carefully designed to deliver controlled, pharmacologically active doses of nicotine to the smoker, including the tobacco blend, the filter, and the ventilation system. *See* section II.C.4., above. Collectively, the drug delivery components of cigarettes are an instrument, implement, contrivance, or similar article that is designed to release a nicotine-containing aerosol, i.e., the tobacco smoke, that, upon combustion outside the body, is inhaled by the smoker and serves as the vehicle for nicotine delivery.

Second, consistent with section 201(h)(3) of the Act, the device components of cigarettes are "intended to affect the structure or any function of the body." Cigarettes are "intended" to deliver nicotine to the body. *See* Section II, above. The nicotine delivered by the device components of cigarettes "affect[s] the structure or any function of the body." *See* Section I, above. The device components of cigarettes are thus designed to achieve the specific purpose of affecting the structure and function of the body by delivering a controlled amount of nicotine to the body.

[1144] *Regulation of Tobacco Products (Part 3): Hearings before the Subcommittee on Health and the Environment, House Energy and Commerce Committee, U.S. House of Representatives*, 103d Cong., 2d Sess. 173 (Jun. 23, 1994). *See* AR (Vol. 709 Ref. 3).

[1145] Response of R.J. Reynolds Tobacco Company, Appendix D, FDA Docket No. 94P-0069 (Nov. 2, 1994), at 78. *See* AR (Vol. 447 Ref. 7640).

Third, as required by the statutory definition, the device components do not achieve their delivery purpose through "chemical action within or on the body." Although the *nicotine* delivered by cigarettes achieves its primary intended purpose through a series of chemical actions inside the body, the device components do not rely on chemical actions within or on the body to achieve their drug delivery purpose. Rather, the device components of cigarettes achieve their primary purpose by delivering nicotine to the body in an aerosol form. This nicotine-containing aerosol is produced by combustion outside the body—not by chemical actions within or on the body.

Fourth, as required by the statutory definition, the device components in cigarettes are not "dependent upon being metabolized" to achieve their primary intended purpose. Metabolism is "the conversion of one chemical species to another."[1146] To be metabolized, most substances must first be ingested or absorbed into the body, where metabolism occurs after the substance reaches the gastrointestinal tract (the liver) or the systemic circulation.[1147] In the case of cigarettes, the nicotine delivered by a cigarette is inhaled and delivered to the bloodstream where it can achieve its intended purpose, before any metabolism takes place. Thus, the device components achieve their primary intended purpose without being metabolized.

Cigarettes are similar to other articles that are routinely regarded as combination products containing both a drug and a drug delivery instrument, apparatus, machine, contrivance, or similar or related article under the Act. In 1991, the Agency's Center for

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[1146] Rowland M, Thomas TN, *Clinical Pharmacokinetics: Concepts and Applications* (Baltimore: Williams & Wilkins, 1995, 3d ed.), at 15. *See* AR (Vol. 711 Ref. 49).

[1147] *See Id.* at 14.

Drug Evaluation and Research and the Agency's Center for Devices and Radiological Health reached an intercenter agreement delineating the types of products that would be considered to have drug and device components. Under this agreement, an article "with [the] primary purpose of delivering or aiding in the delivery of a drug and distributed containing a drug (i.e., 'pre-filled delivery system')" is regarded as a combination product with drug and device components.[1148] The intercenter agreement specifically lists nebulizers, transdermal patches, and pre-filled syringes as examples of "pre-filled delivery systems."[1149] Prefilled intravenous infusion pumps, which are used to deliver drugs to patients intravenously, are another example. Cigarettes are comparable to these articles. Nebulizers and metered dose inhalers are products filled with a drug used by persons with asthma to relieve constricted airways. Like nebulizers and metered dose inhalers, cigarettes contain an instrument, implement, contrivance, or similar or related article for converting a drug into an aerosolized form for inhalation. Cigarettes are also similar to prefilled intravenous infusion pumps, in that drug delivery components of both deliver the drug to the body for absorption, after which the device components are discarded or destroyed.

The internal tobacco company documents themselves recognize that cigarettes should be regarded as nicotine delivery devices. For example, as early as 1972, a senior Philip Morris researcher characterized the cigarette as "*a dispenser for a dose unit of nicotine*" and stated that "[s]moke is beyond question the most optimized vehicle of

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[1148] *Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health* (Oct. 31, 1991), at 6. *See* AR (Vol. 30 Ref. 289).

[1149] *Id.*

nicotine and the cigarette the most optimized dispenser of smoke."[1150] Twenty years later, a Philip Morris official continued to describe cigarettes as "*nicotine delivery devices*," placing "conventional cigarettes" in the same category as nicotine "chewing gums, patches, aerosol sprays and inhalers."[1151]

Researchers at other cigarette manufacturers have expressed similar views. In 1962, a senior BATCO scientist described the advantages of nicotine delivery through cigarettes, stating that "the techniques of administration by smoking ha[ve] considerable psychological advantages and a built-in control against excessive absorption."[1152] Decades later, BATCO researchers continued to characterize cigarettes in device-like terms, describing cigarettes as "the means of providing nicotine doses in a metered fashion"[1153] and as a delivery mechanism that allows "the smoker to have very flexible control over titrating his desired dose of nicotine."[1154] Similarly, in the words of one senior RJR scientist, "a tobacco product is, in essence, *a vehicle for delivery of nicotine*, designed to deliver the nicotine in a generally acceptable and attractive form."[1155]

[1150] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 5-6 (emphasis added). *See* AR (Vol. 12 Ref. 133).

[1151] Philip Morris Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*, at 2 (emphasis added). *See* AR (Vol. 531 Ref. 122).

[1152] Ellis C (BATCO), The smoking and health problem, in *Smoking and Health–Policy on Research*, Research Conference, Southampton, England (1962), at 4. *See* AR (Vol. 21 Ref. 220).

[1153] Proceedings of the BATCO Group R&D Smoking Behaviour-Marketing Conference, Session I, slides (Jul. 9-12, 1984), at BW-W2-03242 (emphasis added). *See* AR (Vol. 24 Ref. 315).

[1154] *Transdermal Nicotine Patches*, at 3. *See* (AR Vol. 531 Ref. 124).

[1155] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 2 (emphasis added). *See* AR (Vol. 531 Ref. 125).

III.B.2.

The history of the manufacturers' product research and development further demonstrates that cigarettes are designed to deliver nicotine to the smoker. As described in section II.C.3., above, the manufacturers have engaged in extensive product research and development for over three decades to optimize the delivery of nicotine from cigarettes. This product research and development has even included the development of novel tobacco products, such as Premier by RJR, that are designed to deliver nicotine to the smoker "by heating, rather than burning, tobacco."[1156] *See* section II.C.3., above.

For these reasons, the Agency has determined that cigarettes are most appropriately considered a prefilled delivery system under the intercenter agreement. They are a combination product under the Act consisting of the drug nicotine and a device for delivering nicotine to the smoker.[1157]

2. Smokeless Tobacco Is a Combination Product

The Agency has also determined that smokeless tobacco is a combination product. First, as required by the statutory definition, smokeless tobacco is an "instrument, . . . implement, contrivance, . . . or similar or related article" for delivering nicotine to the consumer. The principal device component in these products is the processed tobacco, the purpose of which is to deliver the nicotine to the cheek and gum tissue for absorption

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[1156] *Chemical and Biological Studies on New Cigarette Prototypes that Heat Instead of Burn Tobacco* (Winston-Salem NC: R.J. Reynolds Tobacco Co., 1988), at 3. *See* AR (Vol. 107 Ref. 980).

[1157] As discussed in Section II.F., above, the Agency has also determined that processed loose cigarette tobacco, which is used by smokers who roll their own cigarettes, is subject to FDA jurisdiction. Processed loose tobacco has a drug and a device component. As noted in Section II.F., consumers obtain separately the components of a cigarette (e.g., processed loose tobacco and special cigarette papers) and then use those components to assemble their own cigarettes. While these homemade products are more crudely manufactured than those produced by cigarette companies, they perform the same device function of delivering a nicotine-containing aerosol to the body for inhalation by the lungs.

into the body. The processed tobacco provides the nicotine to the consumer's body in a form that is palatable and absorbable, thereby allowing the nicotine to diffuse from the tobacco to the buccal mucosa. Some products also have a device component consisting of a porous pouch that holds the processed tobacco in position in the mouth, controlling the absorption of nicotine into the buccal mucosa.

Smokeless tobacco is placed in the mouth, where it forms a matrix from which nicotine is solubilized and then diffused across the buccal mucous membranes into the bloodstream. Thus, the tobacco matrix is the vehicle for rapidly and efficiently delivering nicotine to the smokeless tobacco user through buccal absorption. Smokeless tobacco is thus similar to other combination products that contain instruments, apparatuses, contrivances, or similar or related articles intended to deliver drugs. For example, smokeless tobacco resembles transdermal nicotine patches. Transdermal nicotine patches are considered combination products under an intercenter agreement.[1158] Similar to transdermal nicotine patches, smokeless tobacco contains an instrument, implement, or similar or related article that brings the nicotine into close contact with body tissue, where it can diffuse through the body's membranes into the bloodstream. Smokeless tobacco is also comparable to prefilled intravenous infusion pumps, in that the drug delivery components of both products deliver a drug to the body and are discarded after drug delivery is complete. This feature distinguishes the delivery device components of smokeless tobacco from drugs. A drug is typically ingested or absorbed in the body; in the case of smokeless tobacco, most of the tobacco in the product is not ingested or absorbed

[1158] *Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health* (Oct. 31, 1991), at 6. *See* AR (Vol. 30 Ref. 289).

by the user and is removed from the mouth. Several aspects of the smokeless tobacco may be engineered by the manufacturer to control the rate and extent of absorption of nicotine, the drug to be delivered. For example, the cut of the tobacco may be altered to affect the rate of diffusion of the nicotine through the buccal mucosa.

Second, consistent with section 201(h)(3) of the Act, the device components of smokeless tobacco are "intended to affect the structure or any function of the body." Smokeless tobacco are "intended" to deliver nicotine to the body. *See* Section II., above. The nicotine delivered by the device components of smokeless tobacco "affect[s] the structure or any function of the body." *See* Section I., above. The device components of smokeless tobacco are thus designed to achieve the specific purpose of affecting the structure and function of the body by delivering a controlled amount of nicotine to the body.

Third, as required by the statutory definition, the device components of smokeless tobacco do not "achieve [their] primary intended purposes through chemical action within or on the body." The *nicotine* in smokeless tobacco achieves its primary purposes through chemical actions in the body. The device components, however, achieve their drug delivery function simply by bringing nicotine into contact with the buccal mucosa. To achieve the drug delivery purpose, the tobacco blend (and pouch, if any) must be placed in the mouth and the nicotine must diffuse away from the tobacco. These are

physical processes, not chemical ones,[1159] that are analogous to the physical processes through which transdermal nicotine patches deliver nicotine to the body.

Fourth, as required by the statutory definition, the device components in smokeless tobacco are not "dependent upon being metabolized." After buccal absorption of nicotine is complete, the remaining tobacco material (and pouch, if any) is expectorated whole. The critical absorption of nicotine does not require the metabolism of any part of the tobacco matrix.

For these reasons, the Agency has determined that smokeless tobacco is a combination product under the Act consisting of the drug nicotine and device components for delivering nicotine to the user.

C. RESPONSE TO COMMENTS

1. Several tobacco industry comments assert that drug delivery systems containing drugs are simply drugs, not combination products. These comments maintain that the Agency's position removes any distinction between the terms "drug" and "device" and could result in drugs in tablet or capsule forms being viewed as a combination product consisting of a drug and a drug delivery device.

Since passage of the Safe Medical Devices Act of 1990, however, the Agency could consider some capsules or tablets as combination products under section 503(g). For example, capsules utilizing osmotic pumps to deliver a drug could be regarded as a

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[1159] *See Webster's Collegiate Dictionary* (Springfield, MA: G&C Merriam, 1977 ed.), at 318; *Remington's Pharmaceutical Sciences* (Easton, PA: Mack Publishing, 1980, 16th ed.), at 1388. *See* AR (Vol. 711 Ref. 50).

combination of a "drug" and a "device." The capsules, emptied of the drug, are not absorbed into the body, but are excreted. The delivery mechanism of these capsules is similar to that of a prefilled syringe. Yet there are basic differences between drug delivery systems like cigarettes and smokeless tobacco, on the one hand, and most drugs in tablet or capsule form, on the other. As discussed in section III.B., above, cigarettes and smokeless tobacco have major physical components that deliver nicotine to the consumer but are not absorbed or metabolized within the body. This is not the case with most tablets and capsules, which are absorbed completely along with the drug they deliver and act "through chemical action within or on the body." These basic differences mean that the Agency's decision to consider cigarettes and smokeless tobacco as combination products is reasonable and will not require the Agency to change its treatment of most products that have been adequately regulated as drugs, and begin to regulate them as combination products. The Supreme Court has recognized that the Agency has the discretion to apply the Act's statutory terms to products that reasonably meet those definitions. The fact that a strained extension of the Agency's analysis could lead to an illogical result will not preclude its use when the use itself is reasonable. *United States v. Sullivan*, 332 U.S. 689, 694 (1948).

2. Tobacco industry comments also argue that cigarettes and smokeless tobacco cannot have device components, because if the Agency is right that nicotine is a drug, the primary intended purpose of a cigarette or a smokeless tobacco product taken as a whole is dependent upon the chemical action of nicotine within the body. According to the comments, if the primary mode of action of a cigarette or a smokeless tobacco product

taken as a whole involves the chemical action of nicotine, the cigarette or smokeless tobacco product cannot meet the statutory definition of a device.

FDA disagrees with these comments. These comments confuse the definition of a device with the definition of a combination product. While it is true that under the statute, a device or device component cannot achieve its primary purpose by chemical action within or on the body, a combination product consisting of a drug and a device very well may. Indeed, Congress enacted section 503(g) of the Act specifically to recognize and address products, for example, that have a device component whose primary intended purpose is to deliver a drug by means other than chemical action or metabolizing action within or on the body, *and* a drug component that achieves its primary intended purpose through chemical action and/or by being metabolized. The statute recognizes that a single product can contain components with interdependent, yet distinct, purposes. Under the interpretation urged by the comments, there could never be a combination product composed of a drug and a device where the primary mode of action of the product is by chemical action. That interpretation is entirely at odds with the statutory language and purpose of section 503(g), as well as with FDA's long-standing practice of regulating as combination products many products containing a drug and a device.